The bone defect may also be treated by introducing a hydrated precursor at the implant site, the hydrated precursor comprising an amorphous calcium phosphate and a promoter and converting the hydrated precursor *in vivo* at the implant site to a hardened poorly crystalline apatitic calcium phosphate and bone is formed at the implant site.

## II. Amendments to the claims.

Claims 1, 2, 3 and 26 have been amended and claims 8 and 17-20 have been canceled. Claims 2 and 3 have been amended to correct a typographical error and to provide clarity to the claim language. Support for amendment of claims 1, 2 and 26 is found throughout the specification. It is submitted that no new matter has been entered upon amendment of the claims.

## III. Rejection of the claims over Chow 5,525,148, CA 87:73954 or CA 113:218168.

Claims 1-16, 21, 22 and 26 stand rejected under 35 U.S.C. §103 as being unpatentable over any of Chow, CA 113:181168 or CA 87:73954. The Examiner suggests that the recited poorly crystalline apatitic (PCA) calcium phosphate may read on some of the crystalline states of the prior art. (Note that claim 3 has been amended to properly refer to Figure 3c and not 3a.) Applicants respectfully disagree.

(A) **With respect to claims 1 and 26 and those dependent thereon, Applicants submit that the recited poorly crystalline apatitic (PCA) calcium phosphate does not read on any of the crystalline states of the prior art calcium phosphate and that, even if it did, there is no teaching or suggestion of a resorption rate characterized in that, when placed in a rat intramuscular site, at least 1 g of the PCA calcium phosphate is at least 80% resorbed within one year.**

(i) CA 87:73954. The remarks made in the paper filed November 13, 1997 arguing for patentability of the claims over CA 87:73954 are maintained and repeated herein. CA 87:73954 is an academic investigation into the chemistry of amorphous calcium phosphate (ACP). There is no overlap of crystalline states between the prior art *amorphous compounds* and the recited poorly crystalline compounds of the invention. An amorphous

calcium phosphate is characterized by a complete lack of crystallinity and a distinctive X-ray diffraction pattern, both of which differ from that of the PCA calcium phosphate used in the instantly claimed method. By way of example, compare Figure 3a (an ACP) with Figure 3c (a PCA calcium phosphate) in the instant specification. Thus, references which disclose formation of an amorphous calcium phosphate in no way anticipate or suggest a poorly crystalline calcium phosphate.

Further there is no teaching or suggestion of introducing the material into a bone site or effecting resorption of the material to form bone at the site wherein the resorption rate is characterized in that, when placed in a rat intramuscular site, at least 1 g of the PCA calcium phosphate is at least 80% resorbed within one year. Without any suggestion of resorbability or the ability to promote bone growth, there is absolutely no motivation for anyone to introduce the material of CA 87:73954 into a bony site as recited in the instant claims.

(ii) CA 113:218168. The remarks made in the paper filed November 13, 1997 arguing for patentability of the claims over CA 113:218168 are maintained and repeated herein.

The reference discusses the preparation of crystalline hydroxyapatite. The high temperature conditions of the reference clearly provide a highly crystalline product. Further there is no teaching or suggestion of introducing the material into a bone site or effecting resorption of the material to form bone at the site wherein the resorption rate is characterized in that when placed in a rat intramuscular site, at least 1 g of the PCA calcium phosphate is at least 80% resorbed within one year. Without any suggestion of resorbability or the ability to promote bone growth, there is absolutely no motivation for anyone to introduce the material of CA 113:218168 into a bony site as recited in the instant claims.

(iii) Chow 5,525,148. The remarks made in the paper filed November 13, 1997 arguing for patentability of the claims over Chow are maintained and repeated herein.

Chow makes no claims to a strongly resorbable calcium phosphate material. Chow states that the material is "resorbable" or "slowly resorbable" (col. 12, lines 27-32). Nowhere is the extent of resorption quantified, nor is the amount of material resorbable

specified. As the present application points out, a number of prior art calcium phosphate compositions have been termed "resorbable", but most are only weakly resorbed. Without additional information, there is no reason to believe that the Chow material would have the resorption characteristics specified in claims 1 or 26.

In order to find additional information to substantiate their belief, the Applicants have searched the literature for descriptions of "resorbable" products provided by the Chow research group. Applicants enclose, as Exhibit I, a copy of "Long Term Follow-Up of Hydroxyapatite Cement (HAC) Implants for Craniofacial Reconstruction" (21st Annual Meeting of the Society for Biomaterial, March 18-22, San Francisco, CA 1995), for which Chow is a co-author and which documents the resorption of a Chow cement. The reference reports "excellent" bone substitution in craniofacial reconstruction and states that the "amount of HAC [hydroxyapatite cement] resorption/bone replacement was greater than 80% at 30 months". Thus, a Chow cement is only 80% resorbed after 2 ½ years (!), which the prior art considers to be "excellent" performance, but which falls outside the resorbability profile of the PCA calcium phosphate of the instant invention.

A second investigation of the resorbability of the Chow material can be found in "Facial Skeletal Augmentation Using Hydroxyapatite Cement" (*Arch. Otolaryngol Head Neck Surgery* **119**:185 (1993)), which is enclosed as Exhibit II. The reference reports that after nine months "the proportion of hydroxyapatite implant replaced by bone and osteoid was 42% and 45%" for two dogs that underwent hydroxyapatite cement implantation at the supraorbital ridges of the cranium. Clearly, such a material does not fall within claims 1 or 26.

Chow also makes no claim to a poorly crystalline apatitic calcium phosphate, although the Examiner suggests that the recited poorly crystalline apatitic (PCA) calcium phosphate may read on the Chow hydroxyapatite product. Applicants have suggested that the hydroxyapatite material of Chow is significantly more crystalline than the poorly crystalline apatitic calcium phosphate of the instant invention; however, nowhere is the nature or extent of crystallization of the Chow material quantified.

In order to find additional information to support their position, the Applicants have searched the literature for descriptions of the hydroxyapatite product provided by the

Chow research group. Applicants enclose, as Exhibit III, a copy of "Setting Reactions and Compressive Strengths of Calcium Phosphate Cements" (*J. Dent. Res.* **69**(12):1852), for which Chow is a co-author. The reference investigates the reaction of a calcium phosphate cement to form a hardened hydroxyapatite. Figure 2 provides the XRD patterns at various intervals during the formation of the product hydroxyapatite. Note the sharp peaks which are present in spectra D, E, F and G, but which are absent from the XRD of the inventive PCA calcium phosphate. Sharp peaks are indicative of a crystalline material which is significantly more crystalline than the recited PCA calcium phosphate (compare, Fig. 3c of the instant specification).

For the foregoing reasons, Applicants submit that the poorly crystalline apatitic calcium phosphate used in the method of the invention is well defined and does not read on other hydroxyapatite or amorphous calcium phosphates of the prior art.

**(B) With respect to claim 2 and those dependent thereon, Applicants submit that there is no teaching or suggestion in the prior art of forming a hydrated precursor and converting the precursor into a hardened poorly crystalline apatitic calcium phosphate.**

(i) CA 87:73954. The remarks made in the paper filed November 13, 1997 arguing for patentability of the claims over CA 87:73954 are repeated herein. CA 87:73954 teaches the formation of ACP, but does not teach or suggest its combination with a second component, i.e., a promoter, to produce a hydrated precursor and converting the hydrated precursor into a harden PCA calcium phosphate.

(ii) CA 113:218168. The remarks made in the paper filed November 13, 1997 arguing for patentability of the claims over CA 113:218168 are maintained and repeated herein. The reference reports on the preparation of a crystalline hydroxyapatite. As in Section III (B)(i), there is no teaching or suggestion of combining the material with a second component, i.e., a promoter, to produce a hydrated precursor and converting the hydrated precursor into a harden PCA calcium phosphate.

(iii) Chow 5,525,148. The remarks made in the paper filed November 13, 1997

arguing for patentability of the claims over Chow '148 are maintained and repeated herein.

There is no teaching or suggestion in Chow '148 of introducing a hydrated precursor which is comprised of an amorphous calcium phosphate and a promoter to an implant site and converting the hydrated precursor to a hardened PCA calcium phosphate at the implant site. In fact, Chow '148 admits that:

> a slurry of DCPD, DCPA, octacalcium phosphate (OCP), *amorphous calcium phosphate* (ACP), α-tricalcium phosphate (α-TCP), β-tricalcium phosphate (β-TCP), or a mixture of these salts *does not produce a setting cement* or act as an effective remineralizing agent. (col. 5, lines 55-59, Chow '148; emphasis added).

Chow teaches that the only way to obtain a setting cement for these materials is to combine them at high phosphate concentrations and/or high pH. Neither of these conditions are encountered under *in vivo* conditions or "at the implant site", as is recited in claim 2 of the instant application.

## IV. Rejection of claims 1-16,21, 22 and 26 over Nagata or Palmer in view of Niwa.

Claims 1-16, 21, 22 and 26 stand rejected under USC 35 §103 as being unpatentable over Nagata or Palmer in view of Niwa. Applicants respectfully traverse the rejection.

**(A) With respect to claims 1 and 26 and those dependent thereon, Applicants submit that physical features exist by which to distinguish the prior art 'crystalline hydroxyapatite' from the poorly crystalline apatitic calcium phosphate used in the method of the invention.**

In the previous communication, applicants pointed out that the materials prepared by either Palmer or Nagata were highly crystalline hydroxyapatites. The Examiner asserts in the current Office Action that Applicants have failed to provide property differences between the claimed poorly crystalline and the discussed highly crystalline calcium phosphate of the prior art.

In fact, the poorly crystalline apatitic calcium phosphate used in the instant method possesses unique physical properties, namely, a "poorly crystalline" microstructure (as demonstrated by x-ray diffraction data) and strong bioresorbability (as demonstrated by the

ability for at least 80% of a 1 g sample of the PCA calcium phosphate to be resorbed within one year when placed in a rat intramuscular site).

The high temperature processes of Palmer and Niwa and the hydrothermal process of Nagata undeniably produce crystalline hydroxyapatite. Crystalline hydroxyapatite has been demonstrated to have *very* poor *in vivo* resorption characteristics. **See, for example,** - Shor, E.C. and Holmes, R.E., "Porous Hydroxyapatite" *Advanced Series in Ceramics* - {Ed. Hench, L.L. and Wilson, J. World Scientific. Singapore} **1:181** (1993)

Niwa fails to provide the requisite teaching and, in fact, teaches away from a bioresorbable hydroxyapatite implant. Niwa states that the "bone tissue [is] formed on the surfaces of the [hydroxyapatite] particles" and that "[a]s a result, an integral structure is formed, where powder particles of the apatite calcium phosphate compound are dispersed in a newly formed bone beam" (col. 8, lines 23-33). There is no teaching or suggestion of resorption of the implant material and subsequent bone growth at the implant site.

In summary, the teachings of Palmer, Nagata and Niwa are distinguished from the instant method in that the materials of the prior art do not facilitate rapid bioresorption, coupled with bone growth at the implant cite. Applicants submit that the claimed procedure is distinguishable from the prior art.

The Examiner has also suggested that the specification includes process details which are not disclosed in the prior art but which are not included in the instant claims. For the reasons provided herein above, applicants submit that the claims as currently pending are distinguishable over the prior art and that the claims do not rely on process details related to improved properties in order to distinguish themselves over the prior art.

**(B) With respect to claim 2 and those dependent thereon, Applicants submit that there is no teaching or suggestion in the prior art of forming a hydrated precursor and converting the precursor into a hardened poorly crystalline apatitic calcium phosphate.**

The remarks made in the paper filed November 13, 1997 arguing for patentability of the claims over the cited references are repeated herein. Palmer teaches the formation of ACP, and its subsequent conversion into highly crystalline hydroxyapatite in a high

temperature process. Nagata reports on the preparation of a crystalline hydroxyapatite in a hydrothermal process. There is no teaching or suggestion of combining either material with a second component, i.e., a promoter, to produce a hydrated precursor and converting the hydrated precursor *in vivo* into a hardened PCA calcium phosphate.

Furthermore, there is no teaching in either Palmer or Nagata of effecting a conversion under *in vivo* conditions. In particular, Palmer converts and ACP by heating at 700-1100 °C. Note that there is no teaching of water to form a hydrated precursor. In a similar vein, Nagata teaches conversion of an ACP in an autoclave under conditions of elevated temperature, e.g., 180 °C, at elevated pressures. Neither of these reaction conditions are particularly amenable to life. Thus, Palmer and Nagata fail to teach a conversion step of a hydrated precursor under *in vivo* conditions.

Niwa does not provide the requisite teaching. Niwa teaches the introduction of a reacted crystalline HA into a bone site. There is no teaching of introducing a precursor, which subsequently is converted *in vivo* to form a PCA calcium apatite.

In conclusion, the combined teachings of Palmer or Nagata in view of Niwa fail to teach the conversion of an ACP-containing hydrate precursor under *in vivo* conditions. Niwa fails to teach or suggest the introduction of a precursor (as compared to an inert reacted product) into a bone site. Further, application of *in vivo* conditions to the reactants of Palmer or Nagata would not result in the hardened PCA calcium apatite recited in claim 2 and those dependent thereon.

**V. Comments re restriction requirement.** Applicants are puzzled by the Examiner's assertion that claims 23 and 24 are not directed to the elected invention, while claims 21, 22 and 26 are considered to be so directed. Claims 23 and 24 depend from claims 21 and 22, respectively, which are considered to be directed to the elected invention. Claims 23 and 24 merely further elucidate materials which meet the features of claims 21 and 22. Clarification is requested.

**VI. Identification of Prior Art Publications.** Applicants provide references which contain calcium phosphate materials which represent examples closest to the poorly

crystalline apatitic calcium phosphate of the invention as requested by the Examiner. The references are enclosed as Exhibits III through VII. The citations are as follows:

Exhibit III: "Setting Reactions and Compressive Strengths of Calcium Phosphate Cements" *J. Dent. Res.* **69** (12):1852 (December 1990)

Exhibit IV: "Porous Hydroxyapatite" Shor, E.C. and Holmes, R.E. (1993) Vol. 1, p. 181

Exhibit V: "Skeletal Repair by in situ Formation of the Mineral Phase of Bone" *Science* **267**:1796 (March 1995)

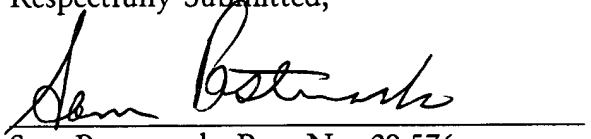
Exhibit VI: "Bone Materials" WO 94/02412

Exhibit VII: "Recent Sutdies of the Mineral Phase in Bone and Its Possible Linkage to the Organic Matrix by Protein-Bound Phosphate Bonds" *Phil. Trans. R. Soc. Lond.* 304:479 (1984).

## Conclusion

For the forgoing reasons, it is submitted that claims 1-7, 9-16, 21, 22 and 26 are in condition for allowance. A Notice the that effect is respectfully requested. Please charge any additional fees or credit any overpayment to our Deposit Account No. 03-1721.

Respectfully Submitted,



Sam Pasternack, Reg. No. 29,576
FOR Mary Rose Scozzafava, Reg. No. 36,268

Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000

Dated: July 16, 1998
DS1.409462.1